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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,066	FIELD ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 29-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the Application filed 18 December 2001 as a continuation of international application PCT/US00/16827, filed 19 June 2000, which claims benefit of US provisional application 60/139,942, filed 18 June 1999. The preliminary amendments filed 18 December 2001 and 14 October 2003 have been entered. Claims 1-48, as originally filed, are pending in the application.

Election/Restrictions

Applicant's election of Group II (claims 20-28) in the Paper filed 8 April 2004 is acknowledged. Because applicant did not distinctly and specifically point out errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-19 and 29-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claim construction

The claims are directed to a cardiomyocyte cell having introduced a nucleic acid encoding a cyclin D2 protein. Although the art recognizes polypeptides comprising SEQ ID NO: 2 or SEQ ID NO: 4 as cyclin D2 proteins, the cyclin D2 protein of the instant claim 20 is clearly not limited to that structure, as evidenced by the structural variants recited in claims 21 and 22. Furthermore, claim 22 limits the cyclin D2 protein of claim 20 to exhibiting "cyclin D2 activity", while the specification provides no explicit definition of what constitutes cyclin D2 activity.

Thus, according to the broadest reasonable interpretation, the cyclin D2 protein of the claims encompasses any protein having some activity in common with the proteins comprising SEQ ID NO: 2 or SEQ ID NO: 4 (*i.e.*, exhibits cyclin D2 activity).

Claim Objections

Claim 20 is objected to because of the following informalities: There is a typographical error in line 1. Specifically, there should be an article between "having" and "introduced". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cardiomyocyte having an introduced nucleic acid encoding a cyclin D2 protein comprising SEQ ID NO: 2, SEQ ID NO: 4 or the sequence of a mouse cyclin D1 protein as described by Soonpa *et al.* (1997) *J. Clin. Invest.* 99:2644-2654 in the paragraph bridging the left and right column on page 2645, does not reasonably provide enablement for a cardiomyocyte cell having introduced a nucleic acid encoding any protein having cyclin D2 activity. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: In their broadest embodiments, the claims encompass a cardiomyocyte having introduced a nucleic acid encoding any protein having cyclin D2 activity, wherein said cyclin D2 activity can be any activity in common with the proteins comprising SEQ ID NO: 2 or SEQ ID NO: 4 (*Id.*). The specification teaches that increasing cyclin D2 activity in cardiomyocyte cells provides enhanced proliferative potential, and utility of the claimed invention is based on the enhanced proliferative potential of the modified cardiomyocytes (see especially the first paragraph on page 4, the first full paragraph on page 5, the paragraph bridging pages 19-20 and the paragraph bridging pages 22-23). Thus, enablement for the full scope of the claims requires that the skilled artisan be able make a cardiomyocyte having an introduced nucleic acid encoding any cyclin D2 protein, wherein said cardiomyocyte has enhanced proliferative potential such that it can be used as contemplated in the specification.

State of the prior art and level of predictability in the art: Soonpa *et al.* (*Id.*) teaches that transgenic mice comprising a cyclin D1 protein expressed in cardiomyocytes exhibit an apparent increase in cardiomyocyte proliferation (see especially the paragraph bridging the left and right column on page 2651). The art does not teach that polypeptides comprising SEQ ID NO: 2 or SEQ ID NO: 4 confer enhanced proliferative potential on cardiomyocytes, and is therefore silent with regard to making a useful cardiomyocyte according to the instant claims beyond a cardiomyocyte comprising the art recognized cyclin D1 polypeptide sequence.

The art does, however, generally teach that the structural determinants of protein function are complex and not well understood. Furthermore, the art teaches that even small changes in protein structure can have dramatic and unpredictable effects on function. For example, Richards (1997) *Cell Mol. Life Sci.* 53:790-802 teaches, "[i]n terms of structural alterations and thermostability, responses to genetic mutations are context dependent and remain difficult to predict with any confidence" (abstract, column 1). Thus, Richards teaches that the effect of mutation on protein stability, a prerequisite for biological function, is unpredictable. Richards also teaches that even limited amino acid modifications can have dramatic effects on protein structure and function. In the second column on page 791, Richards cites the example of influenza virus hemagglutinin protein, wherein alterations in the ionization state of just a few ionizable groups dramatically alters the biological behavior of the molecule. Citing a published study of done on the gene V protein, Richards teaches that, in spite of only limited modification at two amino acid positions, "[t]he effects on the overall stability of the protein were remarkably variable" (page 794, column 1). In the paragraph bridging pages 796 and 797, Richards teaches, "[i]n single site mutants, the structural changes are generally greatest near the site of mutation,

and moving away, decrease radially in all directions. *Even the small changes are so complex that the linkage relations do not allow assignments of the energetic changes to unique parts of the altered residue and its immediate contacts*" (emphasis added) and "[t]here is no convincing explanation yet of how the changes in binding can produce a major movement over such a distance." Finally, in the first full paragraph in the second column on page 793, Richards teaches, "[a]lmost all mutations are accompanied by some conformational change, making prediction of the effects on stability difficult. *In most cases mutations lead to lowering of the stability*." (emphasis added). Thus, Richards teaches that small changes in the primary structure of a protein frequently have dramatic effects on the higher order structure and function of the protein, and that these effects are highly unpredictable.

Given these teachings, the skilled artisan would understand that, without specific guidance as to how a cyclin D1 polypeptide or the polypeptide sequences set forth as SEQ ID NO: 2 or SEQ ID NO: 4 could be modified such that their ability to enhance the proliferative potential of cardiomyocytes is maintained, the utility of cyclin D2 proteins other than cyclin D1 and those comprising SEQ ID NO: 2 or SEQ ID NO: 4 is highly unpredictable. That is, the skilled artisan could not identify which cyclin D2 proteins encompassed by the claims would provide a cardiomyocyte having the useful enhanced proliferative potential without having to empirically test each embodiment. The skilled artisan must therefore rely on the specification to teach how to modify the cyclin D2 protein of the claims such that the full scope of the claimed subject matter can be made and used without undue experimentation.

Amount of direction provided by the inventor and existence of working examples: The working examples of the instant application teach that transgenic mice comprising a cyclin D2

nucleic acid encoding SEQ ID NO: 2 expressed from a cardiomyocyte specific promoter have sustained atrial and ventricular cardiomyocyte DNA synthesis which is increased by isoproterenol (especially example 3) and that cardiomyocytes cultured from the transgenic mouse have enhanced proliferative potential (especially Examples 6, 8 and 9). With regard to modification of the cyclin D2 nucleic acid and protein reduced to practice, the specification merely provides general guidance on nucleic acid and protein modification (see, *e.g.* the discussion beginning in the paragraph bridging pages 11-12). Although the specification suggests modification of certain phosphorylation sites within the cyclin D2 sequence (bridging pages 12-13) and identifies a region of cyclin D2 that is structurally distinct from cyclins D1 or D3 (paragraph bridging pages 13-14), there is no disclosure of the structural requirements for the cyclin D2 enhancement of cardiomyocyte proliferative potential. Thus the teachings of the specification fail to provide the skilled artisan with the means to distinguish useful embodiments of the claimed invention from those that could not be used according to the teachings in the specification short of blind trial and error experimentation.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to make and use the full scope of the claimed invention based on the teachings available at the time of filing without having to engage in undue experimentation. The claims are directed to a cardiomyocyte having introduced a nucleic acid encoding a genus of proteins of broadly divergent structure and function. The specification teaches that at least a subset of the claimed cardiomyocytes would have the useful feature of enhanced proliferative potential but provides no means to predict which of the cardiomyocytes having the structural characteristics set forth in the

claims would have enhanced proliferative potential, other than those expressing SEQ ID NO: 2 and its species homologue SEQ ID NO: 4. As the art teaches that the effect of amino acid sequence modification on protein function is generally unpredictable and the specification provides no specific guidance with regard to how a cyclin D2 protein comprising SEQ ID NO: 2 or SEQ ID NO: 4 can be modified such that it retains the activity that enhances proliferative potential in cardiomyocytes, the skilled artisan would have to resort to undue empirical experimentation to identify the useful embodiments within the scope of the claimed subject matter. For this reason, the disclosure fails to provide enablement for the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is indefinite in reciting, "said introduced nucleic acid has a nucleotide sequence corresponding to nucleotides..." It is unclear what is meant by "corresponding to". Does the nucleic acid actually comprise the sequence defined in the claim or does it correspond to that sequence in some indirect way? If the former is true, the claim should be amended to clearly indicate that the nucleic acid comprises the sequence. If the latter is true, the claim should clearly indicate how the sequence corresponds.

The claim is also indefinite in the recitation of "substantial identity thereto". The phrase is introduced in the paragraph bridging pages 11-12; however, the specification provides no

definition of "substantial identity". It is therefore unclear how the structure of the nucleic acids is limited. For example, is there some threshold of structural identity that is considered substantial or is there a functional component that defines substantial identity? If the latter is the case, what is the functional component and how is it correlated with substantial structural identity? For these reasons, the metes and bounds of the claimed invention are unclear. The claim has been examined with the assumption that any nucleic acid encoding the broad cyclin D2 protein of claim 20 has substantial identity to SEQ ID NO: 1 or SEQ ID NO: 3.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20, 21, 23, 24, 26 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Soonpa *et al.* (1997) *J. Clin. Invest.* 99:2644-2654 as evidenced by Lahti *et al.* (1997) *J. Biol. Chem.* 272: 10859-10869.

Soonpa *et al.* teaches a cardiomyocyte cell having an introduced nucleic acid encoding a cyclin D1 protein (see especially the paragraph bridging the left and right columns on page 2646). As the cyclin D2 protein of the instant claims is construed to encompass any protein having cyclin D2 activity (*Id.*) and Lahti *et al.* demonstrates that cyclin D1 and cyclin D2 have overlapping activity (see especially the paragraph bridging the left and right columns on page

10864), the cyclin D1 protein of Soonpa *et al.* meets the limitations of the cyclin D2 of the instant claims. Therefore, the teachings of Soonpa *et al.* anticipate the instant claim 20. Furthermore, Soonpa *et al.* teach the cardiomyocyte wherein the introduced nucleic acid has "substantial identity" (*Id.*) to nucleotides 4-870 of SEQ ID NO: 1 or SEQ ID NO: 3 according to claim 21; wherein the sequence is operably linked to a constitutive cardiomyocyte specific promoter according to claims 23, 24 and 26 (see especially the paragraph bridging the left and right columns on page 2645); and wherein the cardiomyocyte cell is a mammalian cell according to claim 27.

Soonpa *et al.* teaches a cardiomyocyte comprising all of the limitations of the instant claims; therefore, the claims are anticipated by Soonpa *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

DAVID GUZO
PRIMARY EXAMINER